SUPPORT FOR THE AMENDMENTS

Claims 1-4, 9, 11, 12, and 14 have been amended.

Support for the amendment to Claims 1-4, 9, 11, 12, and 14 is found at pages 1-3 of the specification, the examples, and the original claims.

No new matter has been added.

REMARKS

Claims 1-18 are pending in the present application.

At the outset, Applicants wish to thank Examiner Sullivan and Examiner Richter for the helpful and courteous discussion with their undersigned Representative on April 22, 2009. During this discussion various arguments in traverse of the outstanding rejections and data to demonstrate the differences between the art and the present invention were discussed. The content of this discussion is reflected in the following comments. Reconsideration of the outstanding rejections is requested.

The rejection of Claims 1-18 under 35 U.S.C. §112, second paragraph, is obviated in part by amendment and traversed in part.

Applicants have amended the claims to define the "% by weight" to be on the basis of the total weight of the granulate or composition and to spell out "PEG" as "polyethylene glycol". Thus, the first two criticisms by the Examiner have been overcome and should be withdrawn.

With respect to the allegation that Claim 4 is indefinite for lacking antecedent basis, Applicants disagree. The Examiner's apparent position is that the "granulate" would only contain gabapentin and, therefore, it is unclear how Claim 4 can be definite or how the PEG can be present. Applicants submit that this position underscores a basic misunderstanding on the behalf of the Examiner. In the present invention the gabapentin granulate is identified as such inasmuch as it comprises gabapentin as active ingredient, not that it is the exclusive component as the Examiner appears to allege. It is clear that a gabapentin unit dose (granulate, tablet or capsule) comprises gabapentin in an amount suitable to the specific therapy for which it is to be used and, in addition, all necessary carriers useful for both the

preparation of the pharmaceutical form and to assure efficacy (bioavailability) of the active ingredient when administered to a patient in need thereof.

PEG is one of the carriers and is physical part of the granulate according to the present invention. Actually, PEG acts as granulating agent in a melt granulation process allowing an improved stability of gabapentin (see below). Indeed, the Examiner's attention to the Examples 1-2, which specifically indicate that PEG and the other cited additives are clearly present in the granulate.

Applicants further submit that, contrary to the Examiners' opinion, it is common general knowledge that a granulate can comprise the active ingredient as well as one or more carriers present in different amounts. For instance, the cited art itself describes some gabapentin granulates useful for the preparation of tablets or capsules in terms of ingredients (mg) per unit dose:

a. Manikandan et al. describes gabapentin tablets obtained by compression of a granulate and further excipients. Table on page 3, right column, reports the qualitative/quantitative composition of said tablets by identifying intragranular and extragranular components and relative amounts;

b. Spireas describes (see Examples and, in particular, Tables 2-5) several compositions obtained by wet granulation wherein different kind and amount of excipients are used in the granulation process.

Thus, it is clear that PEG is the granulating agent and as such it is physically present in the granulate of the invention which, in turn, in accordance with common pharmaceutical techniques, may be filled or used, optionally in the presence of further carrier(s) in the preparation of active unit dose being tablets and capsules the preferred ones (see additionally, Examples 3-4 of the present application).

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1-18 under 35 U.S.C. §112, first paragraph (written description), has been indicated as being withdrawn (see Interview Summary).

For sake of completeness, Applicants note that the specification at page 2, lines 9-13 clearly provide written description for a granulate obtained by granulating gabapentin with polyethylene glycol having a melting point comprised between 50 and 80°C. Further, Applicants note that polyethylene glycol is a well-established class of compounds with a well-appreciated structure. Moreover, the Examiner's application of *University of Rochester v. G.D. Searle & Co.*, is misplaced and has no bearing on the claims at issue.

Applicants thank the Examiner for recognizing the sufficiency of the description and indicating in the Interview Summary that this ground of rejection will be withdrawn. Applicants request acknowledgment to this effect.

The rejections of:

(a) Claims 1-5, 7-9, 12, 13, 15, 17, and 18 under 35 U.S.C. §102(e) over Manikandan et al;

(b) Claims 1-13 and 15-18 under 35 U.S.C. §102(b) over Spireas;

(c) Claims 6, 10, 11, and 16 under 35 U.S.C. §103(a) over Manikandan et al in view of Ochiai et al; and

(d) Claim 14 under 35 U.S.C. §103(a) over Manikandan et al in view of Ochiai et al and Patel et al,

are obviated in part by amendment and traversed in part.

Claims 1 and 12 share the following common features: "A gabapentin granulate obtained by *melt* granulating gabapentin with polyethylene glycol having a melting point comprised between 50 and 80°C".

First, as stated above, it is clear that polyethylene glycol is the granulating agent and as such it is physically present in the granulate of the presently claimed invention. The question of whether PEG is contained in the granulate or not is very important in this case. Indeed, at no point do Manikandan disclose or suggest PEG, much less PEG having a melting point between 50 and 80°C. Further, Spireas only disclose PEG 400. Of course, the melting point of PEG increases as molecular weight increases. that PEG 400 has a melting point of only about 4-8°C (see http://en.wikipedia.org/wiki/PEG_400 and the MSDS sheet for polyethylene glycol available at http://www.jtbaker.com/msds/englishhtml/p5029.htm (**copy submitted herewith**)). Clearly, when the claims are properly examined to require that PEG having a melting point between 50 and 80°C to be incorporated in the gabapentin granulate, then Manikandan and Spireas fail to anticipate and/or render obvious the claimed invention, even when consideration is given to Ochiai et al and Patel et al.

Moreover, Applicants submit that the claimed invention is also not anticipated and/or obvious when the product-by-process limitation ("obtained by *melt* granulating gabapentin with polyethylene glycol") is properly taken into account. With respect to the product-by-process limitations of the presently claimed invention, the courts have enunciated that: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claims is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

There are two important aspects to the *In re Thorpe* standard. First, the products in the "product-by-process" claim must be identical or an obvious variant thereof. Second, patentability of a product may not depend on its method of production, but the method of production cannot be disregarded if that method provides a distinct structure or product.

Indeed, the Board and the Courts have said as much, which is set forth in MPEP §2113 in relevant part:

> "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where... the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g. *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)... The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art." (citing *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989)

The foregoing is particularly relevant to the present application, as there are clear differences between the method disclosed by Manikandan et al and Spireas and the method of the present invention.

As stated above, independent Claims 1 and 12 relate to a gabapentin granulate obtained by melt granulating gabapentin with PEG having a melting point comprised between 50 and 80°C. The present invention is characterized in that PEG is the only granulating agent. This specific granulation method, which is carried out in the absence of granulating liquids, allows to obtain a gabapentin granulate endowed with the required different physical properties compared to a standard gabapentin granulate (wet/alcoholic granulation).

First, it is worth noting that granulate of the invention is substantially free of residual solvents being prepared in the absence of any granulating liquid. Being free of residual solvents is an essential feature of the invention by considering that the presence of said solvents in the granulate is one of the main causes of the degradation of the drug. According to the specification, it has been observed that "by granulating with water, under different experimental conditions and with different procedures, the formation of a hydrate is always obtained, with consequent loss in the original crystalline structure" (see page 2, lines 4-6 of the specification).

On the contrary, in the granulate of the present invention gabapentin keeps its original crystalline form. In addition, when gabapentin is granulated according to the present invention, Applicants do not detect the appearance of gabapentin degradation products, calculated through the amount of the known lactam.

Moreover, granulates obtained by melt granulation have optimum sliding and compressibility physical properties (rest angle 30-35% and Carr index 10-18%). Therefore, the above properties, clearly, indicate distinct characteristic of the final granulate that distinguish the structure of the claimed granulate from a granulate obtained by wet granulation as in Manikandan et al and Spireas.

The concept of melt granulation, as well as the absence of solvent as granulating agent, is at least implicitly disclosed in the originally filed application. In fact, inventors themselves located the drawbacks associated with standard granulation with water or industrial granulation with organic solvents (see page 2, lines 3-11). Thus, the technical problem addressed by the present invention is to overcome said drawbacks and, the solution is achieved by a non-standard melt granulation, by avoiding the use of any solvent in the process of the invention.

In addition, experimental work directly and unambiguously discloses the general procedure for the preparation of a granulate according to the invention. Example 1 clearly shows how the mixture containing gabapentin, PEG and, optionally, further additives is heated until the PEG melting point (50-80°C) under stirring and, then, cooled to give the desired stable granulate. No addition of a solvent is required.

To further illustrate that the importance of the process limitation (i.e., melt granulation) Applicants **submit herewith** an executed Declaration under 37 C.F.R. §1.132, which shows physical differences obtained by the process of the present invention.

First, Applicants again point out that it is known in the art that gabapentin compositions suffer from stability concerns including, as noted above, loss of the original crystalline form of the active ingredient and toxic lactam formation.

In this regard, Applicants point to paragraph 6 of the Declaration under 37 C.F.R. §1.132, which provides experimental evidences demonstrating that gabapentin maintains its original crystalline form (crystalline Form II) after the melt granulation process of the present invention (see DSC, FT-IR and FT-Raman analysis). In addition, paragraph 7 of the Declaration under 37 C.F.R. §1.132 refers to wet granulation preliminary trials wherein, as reported in the specification, the formation of a hydrated form of gabapentin has been observed as well as an increase of lactam impurity. In fact, some batches of gabapentin granulate obtained by wet granulation were investigated by FT-Raman analysis; it resulted that all batches prepared contained a different gabapentin polymorphic form i.e. the undesired hydrated one.

Finally, it has been further observed that compositions of the invention are able to maintain the titre of the lactam impurity below 0.2% by weight of gabapentin when subjected to standard stability test (storage conditions of 25°C with 60% of relative humidity and/or of 30°C with 65% of relative humidity) (see paragraph 8 of Declaration under 37 C.F.R. §1.132). Specifically, paragraph 8 of Declaration under 37 C.F.R. §1.132 provides stability date of a specific composition within the scope of the invention, namely:

Gabapentin	88.99%
PEG 4000	4.56%
Starch, pregelatinized	4.45%
Silica, colloidal	0.50%
Magnesium stearate	0.50%

Two batches of the above composition, in a 100 mg and 400 mg capsules formulations, were tested under the above stability conditions. Results in terms of lactam percentage by weight of gabapentin are reported in the following tables:

Batch 154/4 (400mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.4	100.5	101.1	99.4	101.7	100.5
Lactam (% a.i.)	≤0.2	0.014	0.021	0.024	0.027	0.034	0.034

Batch 165/4 (100mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.6	101.6	100.8	101.5	101.3	100.7
Lactam (% a.i.)	≤0.2	0.017	0.020	0.022	0.027	0.029	0.032

These data clearly show that the lactam content of the capsules under standard stability conditions does not exceed reference value i.e. 0.2% by weight of gabapentin. In turn, the above data demonstrates that melt granulating according to the invention allows the preparation of gabapentin pharmaceutical formulations wherein the active ingredient is particularly stable.

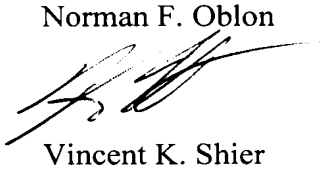
In summary, Manikandan et al and Spireas, even when viewed together with Ochiai et al and Patel et al, fail to anticipate and/or suggest the claimed gabapentin granulate even without specifying the granulation method. However, when further consideration is given to the method by which the granulate is produced, it is without question that any combination of Manikandan et al, Spireas, Ochiai et al, and Patel et al cannot affect the patentability of the claimed invention.

In view of the foregoing, withdrawal of these grounds of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Vincent K. Shier
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)